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STEREOSELECTIVE SYNTHESIS OF β-FLUOROALLYL ALCOHOLS

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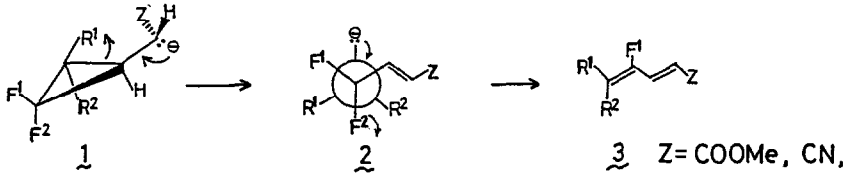
Abstract: β-Fluoroallyl alcohols (6) were obtained with high stereoselectivity by the $LiAlH_4$ reduction of 1-acetoxy-3-alkyl-2,2-difluorocyclopropanes (5).

Fluoroolefins such as fluoroisoprenoids, fluororetinoids and certain fluoroterpenes have been attracting attentions in consideration of their biological activity or their usefulness in the study of biological mechanisms of parent molecules.[1] Although various methods for the preparation of these fluoroolefins have been reported, only a few have shown satisfactory selectivity for constructing fluorinated double bonds.[2] In a previous paper, we reported the stereospecific syntheses of conjugated fluorodienes through a ring-opening reaction of gem-difluorocyclopropane derivatives (1), in which the E-isomer of 1 (R^1=H, R^2=alkyl) gave the (2E, 4E)-fluorodiene (3) and Z-isomer of 1 (R^1=alkyl, R^2=H) gave the (2E, 4Z)-isomer (3), respectively.[3] In this reaction, an α-carbanion (1) may possibly promote ring-opening to form the intermediary carbanion (2) followed by the β-elimination of the fluoride anion through inversion-like mode (Scheme I).

Scheme I

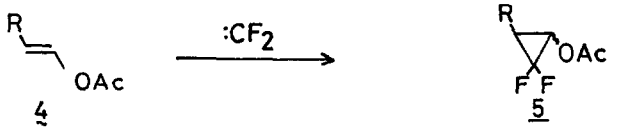


1 2 3 Z= COOMe, CN,

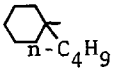
We have also reported that the hydride reduction of acetoxydifluorocyclopropane derivatives provides the corresponding β-fluoroallyl alcohols in good yield,[4] but the stereospecificity of this reaction was not examined in detail. In consideration of the high stereospecificity in the fluorodiene synthesis, the stereochemical aspects of this reaction warrant attention. In this paper, we report on the high stereoselective syntheses of β-fluoroallyl alcohols (5)

through a cyclopropoxide-promoted ring-opening reaction of 1-acetoxy-2-alkyl-3,3-difluorocyclopropane (5) with $LiAlH_4$.

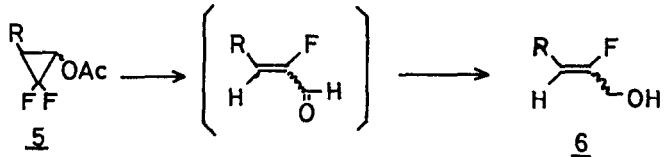
Difluorocyclopropanation of both E- and Z-enol acetate (4) with difluorocarbene ($ClCF_2COONa$, diglyme, 170-180°) proceeded in a stereospecific cis-manner to give the E-cyclopropane [E-5a, ^{19}F-nmr($CDCl_3$) δ +68.0 (dm, J_{F-F}=188 Hz), +93.5 (d, J_{F-F}=188 Hz)] and Z-isomer [Z-5a, ^{19}F-nmr ($CDCl_3$) δ +79.7 (m)], respectively.[5] Similarly, the acetoxydifluorocyclopropanes (5b-5e) were synthesized from the corresponding enol acetates (the ratio of isomers were given in parentheses), isolated and characterized.



4 5

	R	(Z/E ratio)		(Z/E ratio)
E-4a	$PhCH_2$	(8:92)	E-5a	3:97
Z-4a	$PhCH_2$	(100:0)	Z-5a	100:0
4b	n-C_8H_{17}	(60:40)	5b	60:40
4c		(80:20)	5c	80:20
4d	$(n\text{-}C_4H_9)_2CH$	(23:77)	5d	0:100
4e		(0:100)	5e	0:100

Z-β-Fluoroallyl alcohols (Z-6) were obtained with high stereoselectivity by the $LiAlH_4$ reduction of both the E- and Z-isomers of the cyclopropanes (5). Treatment of the Z-isomer (5a) with $LiAlH_4$ in ether at 0°C provided a 93:7 mixture of Z- and E-(6a), while under similar reaction conditions, a 97:3 mixture of E- and Z-(5a) provided a 89:11 mixture of Z- and E-(6a). Furthermore, a stereoisomeric mixture of the cyclopropane (63:37 of Z-5a and E-5a) showed a similar stereoselectivity to give a 90:10 mixture of Z- and E-(6a).[6] The degree of stereoselectivity was found to be affected by the steric bulkiness of the alkyl substituents in the cyclopropanes (see Table) and the reaction of the cyclopropanes with sterically hindered alkyl substituents (entry 8 and 9) proceeded in a completely stereoselective manner, even in these cases the E-cyclopropanes (5d and 5e) were used. A low stereoselectivity was observed in the reaction of 5a with $LiAlH_4$ in diglyme (entry 4) and with red-Al in benzene (entry 5).



5 6

Entry		R	Z/E ratio	Solvent	6 Yield %	Z/E ratio
1[a]	Z-5a	$PhCH_2$	100:0	Et_2O	73	93:7
2[a]	E-5a	"	3:97	Et_2O	71	89:11
3[a]	5a	"	63:37	Et_2O	75	90:10
4[a]	5a	"	43:57	Diglyme	68	69:31
5[b]	5a	"	43:57	Benzene	99	70:30
6[a]	5b	$n\text{-}C_8H_{17}$	40:60	Et_2O	86	85:15
7[a]	5c		20:80	Et_2O	98	81:19
8[a]	5d	$(n\text{-}C_4H_9)_2CH$	0:100	Et_2O	99	100:0
9[a]	5e	 n-Bu	0:100	Et_2O	75	100:0

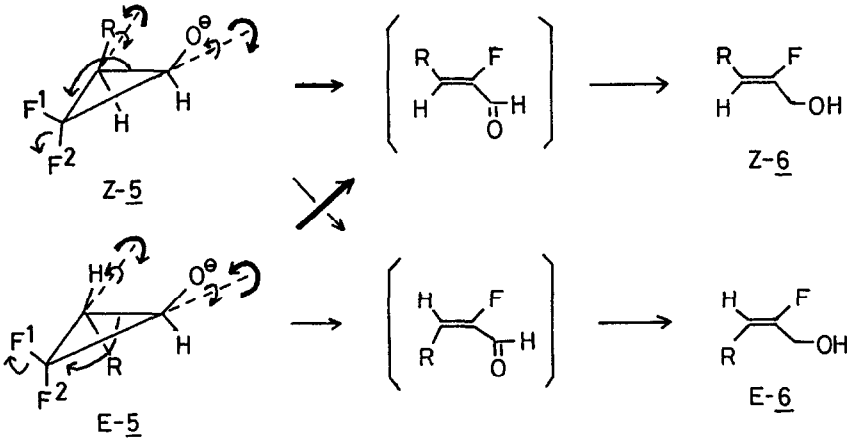
Reagent: a) $LiAlH_4$, b) $Na[AlH_2(OCH_2CH_2OCH_3)_2]$, 3.4M solution in toluene

Although the reaction mechanism could not be completely clarified, the selectivity of the present reaction may possibly involve a sterically favourable ring-opening reaction in which the alkyl substituent on the cyclopropane rotates in an opposite direction toward the cyclopropane plane, regardless of the relative position of the oxygen to the alkyl substituent (R in 5) followed by the elimination of the fluoride (F^2 for Z-5 and F^1 for E-5, respectively) through the inversion-like mode shown in scheme II.[7,8] This similar to the reaction mechanism of 1-chloro-1-fluorocyclopropane derivatives in which the relative position of the leaving chlorine atom and silylalkyl group strongly affects the reaction rate, as was reported by Schlosser et al.,[9] but quite different from that of the fluorodiene synthesis reported presiously.[3]

In conclusion, Z-β-fluoroallyl alcohols (6) are synthesized with high

stereoselectivity by the $LiAlH_4$ reduction of acetoxydifluorocyclopropanes (5). These reactions would provide a new method for the syntheses of fluorinated bioactive compounds and are currently being carried out.

Scheme II



References and Notes

1) R. Filler and S. M. Naqvi, "Biomedicinal Aspects of Fluorine Chemistry"; ed. by R. Filler and Y. Kobayashi, Elsevier Biomedical Press, 1982; pp1-32.
2) M. Schlosser, Tetrahedron, 34, 3(1978).
3) Y. Kobayashi, T. Morikawa, A. Yoshizawa, and T. Taguchi, Tetrahedron Lett., 22, 5297 (1981).
4) Y. Kobayashi, T. Taguchi, M. Mamada, H. Shimizu, and H. Murohashi, Chem. Pharm. Bull. (Tokyo), 27, 3123 (1979).
5) Benzotrifluoride was used as internal standard. + means high field.
6) Z-6a: ^{1}H-n.m.r. ($CDCl_3$) δ 3.44 (2H, d, J=7.5 Hz, $PhCH_2$-), 4.07 (2H, d, J_{H-F}=15 Hz, =$CFCH_2OH$), 5.03 (1H, dt, J_{H-F}=36, J=7.5 Hz, -CH=CF-), 7.25 (5H, s); ^{19}F-n.m.r. ($CDCl_3$) +56 ppm (dt, J=36 and 15 Hz).
E-6a: ^{1}H-n.m.r. ($CDCl_3$) δ 3.33 (2H, d, J=9 Hz, Ph CH_2-), 4.30 (2H, d, J_{H-F}=21 Hz, =CF CH_2OH), 5.40 (1H, dt, J_{H-F}=21, J=9 Hz, -CH=CF), 7.25 (5H, s); ^{19}F-n.m.r. ($CDCl_3$) + 48 ppm (dt, J=21 and 21 Hz).
7) P. Crabbe, J. Luche, J. Damiano, M. Luche, and A. Cruz, J. Org. Chem., 44, 2929 (1979).
8) W. E. Parham, W. D. McKown, V. Nelson, S. Kajigaeshi, and N. Ishikawa, J. Org. Chem., 38, 1361 (1973).
9) M. Schlosser, R. Dahan, and S. Cottens, Helv. Chim. Acta, 67, 284 (1984).

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